ALLOGENEIC TUMOR CELL VACCINE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims priority to U.S. Provisional Application No. 62/425,424, filed on Nov. 22, 2016, the entire contents of which are incorporated by reference in their entirety herein.

FIELD OF THE INVENTION

[0002] The described invention relates generally to immunological approaches to the treatment of cancer, and more particularly to cancer vaccines comprising modified tumor cells.

BACKGROUND OF THE INVENTION

Immune Response

[0003] Generally speaking, immune responses are initiated by an encounter between an individual and a foreign antigenic substance, e.g., an infectious microorganism. The infected individual rapidly responds with both a humoral immune response with the production of antibody molecules specific for the antigenic determinants/epitopes of the immunogen and a cell mediated immune response with the expansion and differentiation of antigen-specific regulatory and effector T-lymphocytes, including both cells that produce cytokines and killer T cells, capable of lysing infected cells. Primary immunization with a given microorganism evokes antibodies and T cells that are specific for the antigenic determinants/epitopes found on that microorganism, but that usually fail to recognize or recognize only poorly antigenic determinants expressed by unrelated microbes (Paul, W. E., "Chapter 1: The immune system: an introduction," Fundamental Immunology, 4th Edition, Ed. Paul, W. E., Lippicott-Raven Publishers, Philadelphia, (1999), at p. 102).

[0004] As a consequence of this initial response, the immunized individual develops a state of immunologic memory. If the same or a closely related microorganism is encountered again, a secondary response ensues. This secondary response generally consists of an antibody response that is more rapid, greater in magnitude and composed of antibodies that bind to the antigen with greater affinity and are more effective in clearing the microbe from the body, and a similarly enhanced and often more effective T-cell response. However, immune responses against infectious agents do not always lead to elimination of the pathogen. (Paul, W. E., "Chapter 1: The immune system: an introduction," Fundamental Immunology, 4th Edition, Ed. Paul, W. E., Lippicott-Raven Publishers, Philadelphia, (1999), at p. 102).

Immune Tolerance of Cancer

[0005] Cancer is characterized by genetic instability of particular cells but has also been described as a disorder of the immune system, based on the fact that the immune system fails, at least in certain segments of the afflicted human population, to respond optimally to cancerous cells that have taken on a distinctly non-self phenotype that should be recognized as foreign. Several reasons have been advanced to explain the basis of this observation. For example, first, cancer cells consist mainly of self-antigens, in striking contrast to the situation with infectious organisms. Some antigens that are classified as cancer antigens are actually normal antigens that are overexpressed, or normal antigens that have a mutation in only one or two amino acids in the polypeptide chain. Second, cancer cells down-regulate Major Histocompatibility Complex (MHC), and thus do not much present tumor cell-derived peptides by way of MHC. Third, cancer cells, and associated tumor-associated macrophages, express cytokines that dampen the immune response (see, e.g., Yu et al (2007) Nature Rev. Immunol. 7:41-51). This dampening is caused, for example, by the secretion of interleukin-10 (IL-10) by the cancer cells or by the associated macrophages. Fourth, unlike the situation with infections, cancer cells do not provide any immune adjuvant. Pathogens express a variety of naturally-occurring immune adjuvants, which take the form of toll-like receptor (TLR) agonists and NOD agonists (see, e.g., Kleinnijenhuis et al (2011) Clin. Dev. Immunol. 405310 (12 pages)). Generally, optimal activation of dendritic cells requires contact of an immune adjuvant with one or more toll-like receptors (TLRs) expressed by the dendritic cell. Without activation of the dendritic cell, contact between the dendritic cell and T cells (immune synapse) fails to result in optimal activation of the T cell.

Immune Surveillance and Immune Editing

[0006] Tumor immune editing is divided into three phases: an elimination phase, an equilibrium phase, and an escape phase. The elimination phase, also known as immune surveillance, is the process by which the immune system identifies cancerous or pre-cancerous cells and eliminates them before they grow out of control. This phase can be complete when all cancerous or precancerous cells are eliminated. If some tumor cells are not eliminated, a temporary state of equilibrium may be achieved between the immune system and tumor cell growth. In this equilibrium phase, tumors cells can either remain dormant or continue to evolve by accumulating further changes to genomic DNA that can modulate the antigens they present. During this process, the immune system exerts a selective pressure on evolving cells, whereby the tumor cells that are less able to be recognized have a survival advantage. Eventually the immune response is unable to recognize cells of the tumor, resulting in the transition to the escape phase wherein tumor cells progressively grow out of control.

Tumor Microenvironment

[0007] The tumor microenvironment provides a consistently effective barrier to immune cell function because tumors actively downregulate all phases of anti-tumor immune responses using a spectrum of different strategies and mechanisms. Many molecular mechanisms that cause dysfunction of immune cells in the tumor microenvironment have been identified, including those directly mediated by factors produced by tumors, and others resulting from alterations of normal tissue homeostasis in the presence of cancer. Most human tumors appear to be able to interfere with one or more stages of immune cell development, differentiation, migration, cytotoxicity and other effector functions (T L Whiteside, The tumor microenvironment and its role in promoting tumor growth, Oncogene (2008) 27, 5904-5912).

[0008] One such mechanism involves accumulation in tumors of T_{reg} ($CD4^{+}CD25^{bright}$ $Foxp3^{+}$ T cells) and